

**AMENDMENTS TO THE CLAIMS**

This listing of claims will replace all prior versions, and listings of claims in the application:

Claims 1-8 (canceled).

Claim 9 (new): An isolated antibody or fragment thereof that binds to mature human TNF $\alpha$ ,

wherein the antibody is characterized in that when the antibody binds TNF- $\alpha$  the induction of endothelial procoagulant activity of TNF- $\alpha$  is inhibited,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-

Ile<sub>155</sub>), or the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155

(Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor.

Claim 10 (new): An antibody or fragment thereof according to claim 9,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-

Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor and wherein the antibody inhibits cytotoxicity.

Claim 11 (new): An antibody or fragment thereof according to claim 9,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-

Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor, and wherein the antibody inhibits tumor regression.

Claim 12 (new): An antibody or fragment thereof according to claim 9,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-

Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor and

wherein the antibody has no effect on cytotoxicity.

Claim 13 (new): An antibody or fragment thereof according to any one of claims 9-12, wherein the antibody is a monoclonal antibody.

Claim 14 (new): An antibody or fragment thereof according to claim 9, wherein the antibody is selected from the group consisting of MAb 1, as produced by hybridoma cell line ECACC Accession No. 89080301, MAb 21, as produced by hybridoma cell line ECACC Accession No. 90012432, MAb 32, as produced by hybridoma cell line ECACC Accession No. 89080302, MAb 42, as produced by hybridoma cell line ECACC Accession No. 89080304, MAb 47, as produced by hybridoma cell line ECACC Accession No. 89121402, MAb 53, as produced by hybridoma cell line ECACC Accession No. 90012433, and MAb 54, as produced by hybridoma cell line ECACC Accession No. 89083103.

Claim 15 (new): An antibody or fragment thereof according to any one of claims 9 - 12, wherein the antibody is a humanized antibody.

Claim 16 (new): An antibody or fragment thereof according to any one of claims 9 - 12, wherein the antibody is a chimeric antibody.

Claim 17 (new): An antibody or fragment thereof according to any one of claims 9 - 12, wherein the antibody is a human antibody.

Claim 18 (new): A composition comprising an isolated antibody or fragment thereof that binds to mature human TNF- $\alpha$ ,

wherein the antibody is characterized in that when the antibody binds to TNF- $\alpha$  the induction of endothelial procoagulant activity is inhibited, wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-

Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>Gln<sub>21</sub>Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-



Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor.

Claim 19 (new): A composition according to claim 18,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-

Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-  
Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-  
Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-  
Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-  
Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155  
(Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-  
Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-  
Ile<sub>155</sub>), is prevented from binding to mature human TNF- $\alpha$  receptor,  
and

wherein the antibody inhibits cytotoxicity.

Claim 20 (new): A composition according to claim 18,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the  
topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-  
Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65  
(Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-  
Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>)  
and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-  
Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18  
(Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-  
Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-  
Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-  
Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the  
topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-  
Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-  
Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-  
Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-  
Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155  
(Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-

Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor, and wherein the antibody inhibits tumor regression.

Claim 21 (new): A composition according to claim 18,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-

Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor and

wherein the antibody has no effect on cytotoxicity.

Claim 22 (new): A composition according to any one of claims 18 - 21, wherein the antibody is a monoclonal antibody.

Claim 23 (new): A composition according to claim 18, wherein the antibody is selected from the group consisting of MAb 1, as produced by hybridoma cell line ECACC Accession No. 89080301, MAb 21, as produced by hybridoma cell line ECACC Accession No. 90012432, MAb 32, as produced by hybridoma cell line ECACC Accession No. 89080302, MAb 42, as produced by hybridoma cell line ECACC Accession No. 89080304, MAb 47, as produced by hybridoma cell line ECACC Accession No. 89121402, MAb 53, as produced by hybridoma cell line ECACC Accession No. 90012433, and MAb 54, as produced by hybridoma cell line ECACC Accession No. 89083103.

Claim 24 (new): A composition according to any one of claims 18-21, wherein the antibody is a humanized antibody.

Claim 25 (new): A composition according to any one of claims 18-21, wherein the antibody is a chimeric antibody.

Claim 26 (new): A composition according to any one of claims 18-21, wherein the antibody is a human antibody.

Claim 27 (new): An isolated single chain antibody that binds to mature human TNF- $\alpha$ , wherein the antibody is characterized in that when the antibody binds to TNF- $\alpha$  the induction of endothelial procoagulant activity is inhibited, wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-

Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor.

Claim 28 (new): An isolated single chain antibody according to claim 27,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-

Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor, and wherein the antibody inhibits cytotoxicity.

Claim 29 (new): An isolated single chain antibody according to claim 27,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or



the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor, and wherein the antibody inhibits tumor regression.

Claim 30 (new): An isolated single chain antibody according to claim 27,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-

Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor and

wherein the antibody has no effect on cytotoxicity.

Claim 31 (new): An isolated single chain antibody according to any one of claims 27 – 30, wherein the antibody is a humanized antibody.

Claim 32 (new): An isolated single chain antibody according to any one of claims 27 – 30, wherein the antibody is a chimeric antibody.

Claim 33 (new): An isolated single chain antibody according to any one of claims 27 – 30, wherein the antibody is a human antibody.

Claim 34 (new): A composition comprising an isolated single chain antibody that binds to mature human TNF- $\alpha$ ,

wherein the antibody is characterized in that when the antibody binds to TNF- $\alpha$  the induction of endothelial procoagulant activity is inhibited,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-

Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-

Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor.

Claim 35 (new): A composition according to claim 34,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-

Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor, and wherein the antibody inhibits cytotoxicity.

Claim 36 (new): A composition according to claim 34,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-

Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), and

wherein the antibody inhibits tumor regression.

Claim 37 (new): A composition according to claim 34,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor and

wherein the antibody has no effect on cytotoxicity.

Claim 38 (new): A composition according to any one of claims 34 – 37, wherein the antibody is a humanized antibody.

Claim 39 (new): A composition according to any one of claims 34 – 37, wherein the antibody is a chimeric antibody.

Claim 40 (new): A composition according to any one of claims 34 – 37, wherein the antibody is a human antibody.

Claim 41 (new): An isolated single domain antibody or fragment thereof that specifically binds to mature human TNF- $\alpha$ ,

wherein the antibody is characterized in that when the antibody binds to TNF- $\alpha$  the induction of endothelial procoagulant activity is inhibited, wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-



Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor.

Claim 42 (new): An isolated single domain antibody according to claim 41,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-

Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor, and wherein the antibody inhibits cytotoxicity.

Claim 43 (new): An isolated single domain antibody according to claim 41,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or

the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor, and wherein the antibody inhibits tumor regression.

Claim 44 (new): An isolated single domain antibody according to claim 41,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-

Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor and

wherein the antibody has no effect on cytotoxicity.

Claim 45 (new): An isolated single domain antibody according to any one of claims 41 – 44, wherein the antibody is a humanized antibody.

Claim 46 (new): An isolated single domain antibody according to any one of claims 41 – 44, wherein the antibody is a chimeric antibody.

Claim 47 (new): An isolated single domain antibody according to any one of claims 41 – 44, wherein the antibody is a human antibody.

Claim 48 (new): A composition comprising an isolated single domain antibody that binds to mature human TNF- $\alpha$ ,

wherein the antibody is characterized in that when the antibody binds to TNF- $\alpha$  the induction of endothelial procoagulant activity is inhibited,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-

Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-

Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor.

Claim 49 (new): A composition according to claim 48,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-

Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor, and wherein the antibody inhibits cytotoxicity.

Claim 50 (new): A composition according to claim 48,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>), 58-65 (Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>), 115-125 (Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>) and 138-149 (Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>), or the topographic region of residues 1-18 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-



Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>) and 108-128 (Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>), or the topographic region of residues 56-79 (Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), or the topographic region of residues 1-20 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>) and 76-90 (Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 69-97 (Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 105-128 (Thr<sub>105</sub>-Pro<sub>106</sub>-Glu<sub>107</sub>-Gly<sub>108</sub>-Ala<sub>109</sub>-Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 135-155 (Glu<sub>135</sub>-Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>-Ile<sub>154</sub>-Ile<sub>155</sub>), and

wherein the antibody inhibits tumor regression.

Claim 51 (new): A composition according to claim 48,

wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic regions of wherein the antibody binds to TNF- $\alpha$  such that the epitope defined by the topographic region of residues 1-30 (Val<sub>1</sub>-Arg<sub>2</sub>-Ser<sub>3</sub>-Ser<sub>4</sub>-Ser<sub>5</sub>-Arg<sub>6</sub>-Thr<sub>7</sub>-Pro<sub>8</sub>-Ser<sub>9</sub>-Asp<sub>10</sub>-Lys<sub>11</sub>-Pro<sub>12</sub>-Val<sub>13</sub>-Ala<sub>14</sub>-His<sub>15</sub>-Val<sub>16</sub>-Val<sub>17</sub>-Ala<sub>18</sub>-Asn<sub>19</sub>-Pro<sub>20</sub>-Gln<sub>21</sub>-Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>), 117-128 (Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>-Lys<sub>128</sub>) and 141-153 (Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>), or the topographic region of residues 22-40 (Ala<sub>22</sub>-Glu<sub>23</sub>-Gly<sub>24</sub>-Gln<sub>25</sub>-Leu<sub>26</sub>-Gln<sub>27</sub>-Trp<sub>28</sub>-Leu<sub>29</sub>-Asn<sub>30</sub>-Arg<sub>31</sub>-Arg<sub>32</sub>-Ala<sub>33</sub>-Asn<sub>34</sub>-Ala<sub>35</sub>-Leu<sub>36</sub>-Leu<sub>37</sub>-Ala<sub>38</sub>-Asn<sub>39</sub>-Gly<sub>40</sub>), 49-97 (Val<sub>49</sub>-Val<sub>50</sub>-Pro<sub>51</sub>-Ser<sub>52</sub>-Glu<sub>53</sub>-Gly<sub>54</sub>-Leu<sub>55</sub>-Tyr<sub>56</sub>-Leu<sub>57</sub>-Ile<sub>58</sub>-Tyr<sub>59</sub>-Ser<sub>60</sub>-Gln<sub>61</sub>-Val<sub>62</sub>-Leu<sub>63</sub>-Phe<sub>64</sub>-Lys<sub>65</sub>-Gly<sub>66</sub>-Gln<sub>67</sub>-Gly<sub>68</sub>-Cys<sub>69</sub>-Pro<sub>70</sub>-Ser<sub>71</sub>-Thr<sub>72</sub>-His<sub>73</sub>-Val<sub>74</sub>-Leu<sub>75</sub>-Leu<sub>76</sub>-Thr<sub>77</sub>-His<sub>78</sub>-Thr<sub>79</sub>-Ile<sub>80</sub>-Ser<sub>81</sub>-Arg<sub>82</sub>-Ile<sub>83</sub>-Ala<sub>84</sub>-Val<sub>85</sub>-Ser<sub>86</sub>-Tyr<sub>87</sub>-Gln<sub>88</sub>-Thr<sub>89</sub>-Lys<sub>90</sub>-Val<sub>91</sub>-Asn<sub>92</sub>-Leu<sub>93</sub>-Leu<sub>94</sub>-Ser<sub>95</sub>-Ala<sub>96</sub>-Ile<sub>97</sub>), 110-127 (Glu<sub>110</sub>-Ala<sub>111</sub>-Lys<sub>112</sub>-Pro<sub>113</sub>-Trp<sub>114</sub>-Tyr<sub>115</sub>-Glu<sub>116</sub>-Pro<sub>117</sub>-Ile<sub>118</sub>-Tyr<sub>119</sub>-Leu<sub>120</sub>-Gly<sub>121</sub>-Gly<sub>122</sub>-Val<sub>123</sub>-Phe<sub>124</sub>-Gln<sub>125</sub>-Leu<sub>126</sub>-Glu<sub>127</sub>) and 136-153 (Ile<sub>136</sub>-Asn<sub>137</sub>-Arg<sub>138</sub>-Pro<sub>139</sub>-Asp<sub>140</sub>-Tyr<sub>141</sub>-Leu<sub>142</sub>-Asp<sub>143</sub>-Phe<sub>144</sub>-Ala<sub>145</sub>-Glu<sub>146</sub>-Ser<sub>147</sub>-Gly<sub>148</sub>-Gln<sub>149</sub>-Val<sub>150</sub>-Tyr<sub>151</sub>-Phe<sub>152</sub>-Gly<sub>153</sub>) is prevented from binding to mature human TNF- $\alpha$  receptor and

wherein the antibody has no effect on cytotoxicity.

Claim 52 (new): A composition according to any of claims 48 – 51, wherein the antibody is a humanized antibody.

Claim 53 (new): A composition according to any of claims 48 – 51, wherein the antibody is a chimeric antibody.

Claim 54 (new): A composition according to any of claims 48 – 51, wherein the antibody is a human antibody.